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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/775,967	02/02/2001	Andrei P. Guzaev	ISIS-4682	9641

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EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 11/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/775,967	GUZAEV ET AL.	
	Examiner	Art Unit	
	Patrick T. Lewis	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,11-15,21,36-40,47-52,56-60,66,81-85,92-101,103 and 104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,11-15,21,36-40,47-52,56-60,66,81-85,92-101,103 and 104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 February 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *11162004* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Advisory Action Dated August 8, 2004

1. The Advisory Action dated August 8, 2004 has been vacated. Applicant's Response dated July 22, 2004 has been considered.

2. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

Election/Restrictions

3. Applicant's election with traverse of the species wherein D^+ is a protonated aromatic heterocyclic amine and E^- is tetrazolide anion in the reply filed on December 24, 2002 is acknowledged. The requirement was made FINAL in the Office Action dated June 11, 2003.

Applicant's Response dated July 22, 2004

4. In the Response filed July 22, 2004, applicant presented arguments directed to the rejection of claims 1-6, 11-15, 21, 36-40, 47-52, 56-60, 66, 81-85, 92-101, 103, and 104 under 35 U.S.C. 103(a).

5. Claims 1-6, 11-15, 21, 36-40, 47-52, 56-60, 66, 81-85, 92-101, 103, and 104 are pending. An action on the merits of claims 1-6, 11-15, 21, 36-40, 47-52, 56-60, 66, 81-85, 92-101, 103, and 104 is contained herein below.

6. Applicant's arguments with respect to claims 1-6, 11-15, 21, 36-40, 47-52, 56-60, 66, 81-85, 92-97, and 104 under 35 U.S.C. 103(a) have been considered but are moot in view of the new ground(s) of rejection.

Rejections of Record Set Forth in the Office Action Dated May 27, 2004

7. Claims 98-101 and 103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caruthers et al. Proceedings of the 2nd International Symposium on Phosphorous Chemistry Directed Towards Biology (1987), pages 3-21 (Caruthers) in combination with Nurminen et al. J. Chem. Soc., Perkin Trans. 2 (1999), pages 2551-2556 (Nurminen).

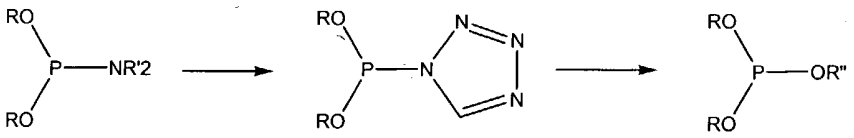
Response to Applicant's Arguments

8. Applicant's arguments filed July 22, 2004 have been fully considered but they are not persuasive. Applicant argues: 1) Caruthers does not teach a process utilizing unprotected internucleoside linkages and 2) Nurminen, while discussing DNA synthesis generally, does not show equivalent reactions for DNA synthesis.

The examiner disagrees with applicant's characterization of Caruthers. Caruthers teaches that the ortho-methylbenzyl phosphite protecting group was removed rapidly and quantitatively during oxidation with I_2 (page 14). The observation prompted the investigation of the ortho-methylbenzyl protecting group for DNA synthesis. Conceivably this group could therefore be removed during the cyclic oxidation step. Consequently the deprotection protocol would be quite simple and consist only of a

concentrated ammonium hydroxide deprotection step. Additionally, one would not expect the accumulated internucleotide phosphate diester to inhibit further elongation of DNA. This is because the mixed anhydride formed from deoxyoligonucleotide phosphate diesters and the deoxylnucleoside 3'-phosphoramidite would, during activation with excess tetrazole, be preferentially cleaved to reform the tetrazolide. Appropriately protected deoxynucleoside 3'-N,N-diisopropylamino-o-methylbenzylphosphoramidites were tested as synthons for deoxyoligonucleotide synthesis. The steps involved in one complete elongation cycle are summarized in Table 5. Thus the deoxynucleoside phosphoramidites were prepared *in situ* as 0.1 M solutions in dry acetonitrile. Aliquots containing a 20-fold excess of the phosphoramidite and tetrazole were added sequentially to a suspension of the deoxynucleoside attached covalently to silica. After completion of the synthesis, amino protecting groups were removed with concentrated ammonium hydroxide and the product purified using standard procedures.

The examiner further disagrees with applicant's characterization of Nurminen. One of ordinary skill in the art would recognize the alcoholysis of dialkyl tetrazolyphosphonites as a model for DNA synthesis. Nurminen teaches that modern automated synthesis of DNA utilizes the reactive phosphoramidites **1**, the dialkylamino



1 **2** **3**

group of which may be easily displaced by the entering sugar hydroxyl function in the presence of an acidic activator. Amine hydrohalides and azoles are known to catalyze the reaction and the most commonly applied catalyst is tetrazole, which is in principle capable of acting as both an acid and a nucleophile. Intermediary formation of tetrazolylphosphonites **2** has been detected during tetrazole-promoted alcoholyses of **1** and they are usually considered to be intermediates of the reaction. Nurminen further teaches that ammonium azolide salts were found to be considerably more efficient catalysts than the corresponding azole acids or tertiary amine bases. Suitable tetrazole and ammonium tetrazolide salts are shown in Table 1.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. Claims 1-6, 11-15, 21, 36-40, 47-52, 56-60, 66, 81-85, 92-97, and 104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caruthers et al. Proceedings of the 2nd International Symposium on Phosphorous Chemistry Directed Towards Biology (1987), pages 3-21 (Caruthers) in combination with Nurminen et al. J. Chem. Soc., Perkin Trans. 2 (1999), pages 2551-2556 (Nurminen).

Claims 1-6, 11-15, 21, 36-40, and 47 are drawn to a method comprising reacting a nucleoside phosphoramidite with a support bound oligomer in the presence of a neutralizing agent, wherein said neutralizing agent is an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, a guanidine, or a salt of formula D^+E^-. Claims 48-52, 56-60, 66, 81-85, 92-95, and 104 are drawn to a method of forming an internucleoside linkage in the presence of a neutralizing agent, wherein said neutralizing agent is an aliphatic amine, an aliphatic heterocyclic amine, an aromatic amine, an aromatic heterocyclic amine, a guanidine, or a salt of formula D^+E^-. Claims 96-97 are drawn to a method comprising the steps of: a) providing a solid

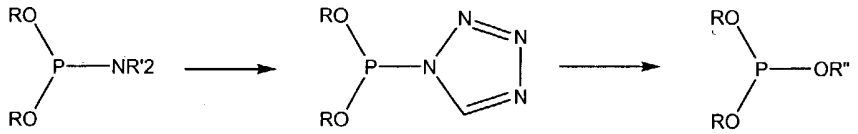
support having a 5'-O-protected phosphorous-linked deprotecting the 5'-hydroxyl of the oligomer bound thereto; b) protected oligomer; c) optionally washing the deprotected phosphorous-linked oligomer on the solid support; d) contacting the support bound oligomer with a solution comprising a 5'-protected nucleoside phosphoramidite and a neutralizing agent; and e) oxidizing or sulfurizing the phosphite triester linkage.

Caruthers teaches that the ortho-methylbenzyl phosphite protecting group was removed rapidly and quantitatively during oxidation with I_2 (page 14). The observation prompted the investigation of the ortho-methylbenzyl protecting group for DNA synthesis. Conceivably this group could therefore be removed during the cyclic oxidation step. Consequently the deprotection protocol would be quite simple and consist only of a concentrated ammonium hydroxide deprotection step. Additionally, one would not expect the accumulated internucleotide phosphate diester to inhibit further elongation of DNA. This is because the mixed anhydride formed from deoxyoligonucleotide phosphate diesters and the deoxylnucleoside 3'-phosphoramidite would, during activation with excess tetrazole, be preferentially cleaved to reform the tetrazolide. Appropriately protected deoxynucleoside 3'-N,N-diisopropylamino-o-methylbenzylphosphoramidites were tested as synthons for deoxyoligonucleotide synthesis. The steps involved in one complete elongation cycle are summarized in Table 5. Thus the deoxynucleoside phosphoramidites were prepared *in situ* as 0.1 M solutions in dry acetonitrile. Aliquots containing a 20-fold excess of the phosphoramidite and tetrazole were added sequentially to a suspension of the deoxynucleoside attached covalently to silica. After completion of the synthesis, amino

protecting groups were removed with concentrated ammonium hydroxide and the product purified using standard procedures.

Caruthers differs from the instantly claimed invention in that Caruthers does not teach the use of a neutralizing agent of D^+E^-; however, the use of a neutralizing agent of the formula D^+E^- as a suitable replacement for tetrazole would have been obvious to one of ordinary skill in the ad when the teachings of Nurminen are considered.

Nurminen teaches that modern automated synthesis of DNA utilizes the reactive phosphoramidites **1**, the dialkylamino group of which may be easily displaced by the



entering sugar hydroxyl function in the presence of an acidic activator (page 2551). Amine hydrohalides and azoles are known to catalyze the reaction and the most commonly applied catalyst is tetrazole, which is in principle capable of acting as both an acid and a nucleophile. Intermediary formation of tetrazolylphosphonites **2** has been detected during tetrazole-promoted alcoholyses of **1** and they are usually considered to be intermediates of the reaction. Nurminen further teaches that ammonium azolide salts were found to be considerably more efficient catalysts than the corresponding azole acids or tertiary amine bases (Abstract, Fig. 2, Fig. 3). For instance, the relative rates obtained with N,N-diisopropylethylammonium tetrazolide, N,N-diisopropylethylamine and tetrazole were 104, 28 and 1 , respectively. The salts of

strong protolytes are better catalyst than those of weak ones. Other suitable tetrazole and ammonium tetrazolide salts are shown in Table 1.

It would have been obvious to one of ordinary skill in the ad at the time of the invention to replace tetrazole with an ammonium azolide salt in the process taught by Caruthers as Nurminen expressly provides motivation for doing so [ammonium azolide salts were found to be considerably more efficient catalysts than the corresponding azole]. The examiner finds one of ordinary skill in the ad as being a PhD in the field of nucleoside/nucleotide synthesis. Based on the teaching of Nurminen, the skilled artisan would have a reasonable expectation of success in substituting tetrazole with an ammonium azolide salt to form internucleoside linkages. The selection of a known material based on its suitability for its intended use is well within the purview of one of ordinary skill in the art at the time of the invention and is prima facie obvious.

Conclusion

13. Claims 1-6, 11-15, 21, 36-40, 47-52, 56-60, 66, 81-85, 92-101, 103, and 104 are pending. Claims 1-6, 11-15, 21, 36-40, 47-52, 56-60, 66, 81-85, 92-97, and 104 are rejected. No claims are allowed.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 571-272-0655. The examiner can normally be reached on Monday - Friday 10 am to 3 pm (Maxi Flex).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patrick T. Lewis, PhD
Examiner
Art Unit 1623

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